II. REMARKS

Claims **53-57, 59-61, 63-64, 68-70 and 79-93** are pending in the subject application and were examined. By this Amendment, claims **53-57, 59-61, 65-67, 81, 82, 84 and 91-93** have been canceled without prejudice or disclaimer. Claims **63, 68, 69, 79, 80 and 85** have been amended and new claims **94** through **99** have been added. Applicants' cancellation of claims and the amendment of the claims as previously presented are made without prejudice to Applicants' right to pursue the same or similar claim in a related application. The cancellation of these claims and the amendment of the claims are not intended to be a dedication to the public of the subject matter of the claims as previously presented.

The claim amendments and the addition of new claims **94** through **99** do not raise an issue of new matter. Support for the amendments is found in the application papers on pages 26, 27, 36, 37 and 68 to 70. Entry of these amendments is respectfully requested.

This Amendment changes and deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejections is respectfully requested. After amending the claims as set forth above, claims **63, 64, 69, 70, 79, 80, 83, 85-90** and **94** to **99** are presently pending and under examination.

Summary of Examiner Interview

Applicants' representative thanks the Examiner for the courtesy extended during the June 12, 2007 personal interview. In accordance with the procedure outlined in M.P.E.P. § 713.04, the following is a summary of the interview.

1. A brief nature of any exhibits shown or any demonstration conducted: No exhibits were shown nor was any demonstration conducted.

2. An identification of the claims discussed: All pending claims were discussed.

3. An identification of the prior art discussed: Prior art was not discussed as no art, other than the assignee's copending applications, has been raised under 35 U.S.C. § 102 or 103.

4. An indication of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner: No specific claim amendments were proposed other than amendment of the claims to specific cell types and/or cancers.

5. A brief description of the general thrust of the principal arguments presented to the Examiner: The thrust of the interview was the basis for removal of the 35 U.S.C. § 112 rejections for the full scope of the claims. The undersigned attorney advised the office that the rejection of the claims was improper as the evidence of record shows that the claims are commensurate with the record. Applicants' attorney discussed the reasons why the scope of the claims are enabled through their full scope. Applicants have shown the mechanism of action of the claimed compounds, namely that they are prodrugs activated by thymidylate synthase (TS). TS is known to be overexpressed in certain cancer cells and the claims are specific to cells endogenously

overexpressing TS. Because the records shows that TS causes the conversion of the prodrug to the toxic metabolite, there is an expectation that the growth or proliferation of any cell overexpressing TS would be inhibited by contacting this cell with a compound defined in the claims.

6. A general indication of any other pertinent matters discussed: Applicants' attorney reviewed the subject matter of the present application in relation to the copending co-owned applications that have been cited by the Examiner under obviousness-type double patenting and pointed out for the Examiner's convenience the commonalities and differences among the applications.

7. If appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the Examiner: Applicants' attorney offered claim amendments but the Examiner did not opine the acceptability of these offered claim amendments to remove the outstanding rejections.

35 U.S.C. § 112, First Paragraph

Claims **60, 63-64, 68-70, 79-80 and 83-93** stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Without repeating the grounds for rejection, the Office stated that the fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation.

The Office further stated that claims **87-90** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. §112.

Without conceding the correctness of the Office's position and to advance allowance of the claims, the compound claims have been amended to derivatives of

compound NB1011 and its parent compound, wherein the derivative compounds are uridylates with a 5-divinyl substituent. With respect to the claims which are directed to use of the compounds, the claims have been amended to recite specific cell types or cancers containing specific cancer cells or tissue and therefore do not more broadly claim the use of the compounds against pathological cells. The newly added claims are of similar scope.

In paragraph "A" on page 2 of the Action, the office questioned the enablement of the isomeric form of the claimed compounds and support for the extension of the use of the compounds to treat liver cancer.

The compounds of this invention are active against cells that overexpress thymidylate synthase. Although Applicants' specification does not show data that the compounds were tested for activity against liver cancer cells overexpressing TS, it does show that the compounds are active against breast and colon cancer (see Table 5 on pages 68 and 69 of Applicant's specification). Liver cancer also is known to contain cells and/or tissue that overexpress TS. See, for example, Libra et al. (2004) *Thymidylate synthase mRNA levels are increased in liver metastases of colorectal cancer patients resistant to fluoropyrimidine-based chemotherapy*, BMC Cancer **4**:11 (copy enclosed) and references cited therein. Thus, there is no reason to doubt that the compounds would be equally active against liver cancer since there is a common pathology present among liver cancer, breast cancer and colon cancer, namely the overexpression of TS.

With respect to the form of the isomer, Example 12 on pages 54 and 55 of the specification teach one of skill in the art to isolate the isomers which were initially prepared as racemic mixtures. Applicants' invention does not require that the isomers be isolated prior to administration and the data shown in Table 5 of the specification

was not generated by only one isomer. Therefore, amendment of the claims to any particular isomer is incommensurate with the teachings of Applicants' specification.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections are respectfully requested. Applicants also wish to submit that Office's reliance on *Ex parte Balzarini*, 21 USPQ2d 1892 (BPAI 1992)[1], as legal support for the rejection under 35 U.S.C. § 112, first paragraph is misplaced. Applicants submit that the facts underlying this decision distinguish the holding and make reliance on this decision improper in support of the present rejection.

The claims under consideration in *Balzarini supra*, were to the use of certain claimed compounds to treat retroviral infections. More particularly, the claims were directed to methods to treat or inhibit HIV infections and to treat diseased caused by HIV, most notably AIDS and AIDS-related disorders. The Office initially rejected the claims under 35 U.S.C. § 101 and § 112, first paragraph on the ground that *in vitro* evidence of record did not support the use of the compounds *in vivo*. However, unlike the facts of the present application, the Office supplied a published technical opinion supporting the contention that the *in vitro* evidence in the specification (further supported by an opinion declaration) was insufficient to establish enablement of the methods *in vivo*. In affirming the Office's rejections, the Board noted that:

> "It is apparent from this reference [Sandstrom, supplied by the Office in rebuttal of the statements made by Applicants] that in 1987 those skilled in this art did not associate successful *in vitro* treatment of HIV infected human cells with any probability of achieving success in *in vivo* treatment of this disease. While the *in vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy. As set forth on page 386 of Sandstrom in the conclusion section, the development of *in vitro* assay systems is important

[1] See page 4 of the Office Action issued April 10, 2007.

> in this area so that "national selection of potential anti-viral compounds can be made" (emphasis added).
>
> The difficulty in concluding that a specific anti-viral compound will be useful *in vivo* in this field solely from *in vitro* testing is particularly seen from the results set forth in Sandstrom for the anti-viral compounds suramin and AZT. Suramin is a known antiviral agent which was demonstrated by Mitsuya in 1985 to protect human T-cells against infectivity and cytopathic effects of HIV *in vitro*. The authors state in the second full paragraph of this article their belief that the *in vitro* results reported in this reference provide a rationale for a "carefully-monitored experimental trial" of this anti-viral compound in patients with AIDS to determine whether suramin does inhibit HIV replication *in vivo*. Thus, even the researchers who performed the work establishing the *in vitro* efficacy of suramin against HIV infected human cells were unwilling to predict that such *in vitro* work provided a basis to conclude that this compound would have *in vivo* efficacy."
>
> *Id.* at 1895.

In contrast to the facts of *Balzarini*, *supra*, Applicants are neither claiming the treatment of retroviral infections and AIDS nor has the Office provided reasoned technical evidence why one of skill in the art would question the evidence of record showing how to make and use the claimed invention within the full scope of the claims.

Applicants amended claims are directed to compounds and their uses in treating specified cancers or inhibiting the growth of a specified cancer cell type. All cells and tissue are related in that the cells or tissue overexpress thymidylate synthase (TS). Unlike the treatment of HIV infections and AIDS, the successful treatment of cancer is no longer considered incredible. Rather, the successful treatment of many cancers has been documented and the correlation between *in vitro* and *in vivo* efficacy also has been documented. Applicants also have shown that the claimed compounds are prodrugs that are converted to the active metabolite by the enzyme TS. TS was known to be overexpressed in cancers (see Table 3 on pages 65 and 66 of Applicants' specification and pages 73 and 75 of Applicants' co-pending application, U.S. Serial No. 10/048,033). A representative class of the compounds were shown to be inhibit the

growth of cancer cells *in vitro* (see Table 5 on page 68). The activities of these compounds were compared to the parent NB 1011 compound which also has been shown to be active across of range of cancer cell types. For these reasons, the reliance on *Balzarini, supra*, is misplaced and rejection should not be maintained against the amended claims. An indication of allowable subject matter is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims **54-56** stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office stated that in claims **54-56** the term "E" and "Z" are not properly applied because the 5'-substituent has two E/Z alternative opportunities.

Without conceding the correctness of the Office's position, the claims have been canceled thereby rendering the rejection moot.

Double Patenting

Claims **53-57, 59-61, 63-64, 69-70, 79-86 and 91-93** stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims ***1-10*** of U.S. Patent No. **6,683,061**. Although the conflicting claims are not identical, they allegedly are not patentably distinct from each other because the method of treatment and alleged active ingredients are directed to substantially overlapping subject matter. Applicants will defer responding to this Action until allowance of a claim has been indicated by the Office.

In accordance with the duty of disclosure set forth in M.P.E.P. § 2001.06(b), Applicants note the following co-pending applications and issued patents for the

Examiner's convenience:

1. U.S. Patent No.: 6,495,553, U.S. Serial Nos.: 09/782,721, 11/034,036; 09/789,226; and 11/627,341;

2. U.S. Patent Nos.: 6,339,151 and 6,245,750;

3. U.S. Serial No.: 10/048,033;

4. U.S. Patent No.: 6,683,061;

5. U.S. Patent No.: 7,138,388 and U.S. Serial No.: 11/516,457; and

6. U.S. Serial No.: 10/119,927.

Supplemental Information Disclosure Statement

Attached to this Reply is a Supplemental Information Disclosure Statement and accompanying reference. Consideration and entry into the file is respectfully requested.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the

Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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